REMARKS

I. Status of the Claims

Claims 1-10 and 21 were pending at the time the Office Action dated May 12, 2009 ("the Action"), was mailed. Claim 1 is amended as discussed below. No new matter is introduced by this amendment. Claims 1-10 and 21 remain pending.

II. The Written Description Rejection of Claim 6 Is Overcome

The Examiner maintains the written description rejection of Claim 6, asserting that because the specification provides only one preferred example of a species that falls within the genus of "dielectric material" as recited in this claim, possession of the invention as claimed is not apparent. Applicants respectfully disagree.

As noted in applicants' previous response and acknowledged by the Examiner, the present specification provides a definition of a dielectric material on p 6: it is a material that, "when exposed to microwaves, increases in temperature in proportion to power applied." While the specification may provide only one example of such a material, the Examiner has not put forth adequate reasoning to assert that this example, in conjunction with the definition provided, is insufficient to satisfy the written description requirement. *See* M.P.E.P. § 2163 (the Examiner has the initial burden of presenting by a preponderance of evidence why a skilled artisan would not recognize in an applicant's disclosure a description of the invention defined by the claims).

"The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species...." M.P.E.P. § 2163. This section of the M.P.E.P. elaborates as follows:

> What constitutes a 'representative number' is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a 'representative number' depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the

LAW OFFICES OF
CHRISTENSEN O'CONNOR JOHNSON KINDNESS PLLC
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

> elements possessed by the members of the genus in view of the species disclosed.

Id. The Examiner has provided no facts that state or suggest that the level of skill and knowledge in the art of dielectric materials renders the recitation of additional species in the specification necessary to satisfy the written description requirement. *See id.* ("Compliance with the written description requirement is essentially a fact-based inquiry that will 'necessarily vary depending on the nature of the invention claimed.'" (quoting *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 323 F.3d 956, 963 (Fed. Cir. 2002)). Because the Examiner has failed to provide "a reasonable basis to challenge the adequacy of the written description," a *prima facie* case has not been established and the rejection cannot stand. See M.P.E.P. § 2163.

In addition to applicants' showing that a *prima facie* case has not been established, applicants also assert that disclosure of one species satisfies the written description requirement in this case. With respect to satisfying the written description requirement, "there may be situations where one species adequately supports a genus." *Id.* Such a case is *In re Herschler*, where a claimed genus of "physiologically active steroids" was adequately described by the provision of a definition of "physiologically active substance" as well as an example of a physiologically active steroid. 591 F.2d 693, 700-703 (CCPA 1979). The facts here are similar to *Herschler*, as a definition of "dielectric material" is provided along with an example. Moreover, the *Herschler* court emphasized that the applicants in that case were not attempting to claim new physiologically active steroids and, as such, this genus was "auxiliary" to the invention. *Id.* at 701-702. In this regard, the court noted,

> In sum, claims drawn to the use of known chemical compounds in a manner auxiliary to the invention must have a corresponding written description only so specific as to lead one having ordinary skill in the art to that class of compounds. Occasionally, a functional recitation of those known compounds in the specification may be sufficient as that description.... [S]uch is the case [here].

LAW OFFICES OF
CHRISTENSEN O'CONNOR JOHNSON KINDNESS PLLC
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

Id. at 702. Not only are the present inventors not attempting to claim new species of dielectric materials such that their claimed use is auxiliary to the invention, but the definition of "dielectric material" provided by the present specification is also functional in nature: these similarities further strengthen the applicability of the rationale and outcome of *Herschler* here.

For at least the reasons discussed above, applicants have shown that the genus of dielectric materials presently claimed satisfies the written description requirement. Withdrawal of the rejection of Claim 6 is respectfully requested.

III. The Enablement Rejection of Claims 1-10 Is Overcome

Claims 1-10 are newly rejected under 35 U.S.C. § 112, first paragraph, as failing the enablement requirement. In particular, while the Examiner concedes that the specification is enabling for cyclodextrins and maltodextrins as described on pages 4-5 of the specification as a "limited class" of water-soluble complexing agents, the specification is said not to enable the practice of the invention with respect to the genus of "water-soluble complexing agents" as recited in Claim 1. Action, page 6.

Applicants respectfully disagree. There is no evidence or reasoning to support a contention that the breadth of the genus is not enabled, or that the specification provides insufficient guidance for practicing the claimed invention with respect to this genus, or that this genus suffers from unpredictability such that additional enabling disclosure is required. As such, the enablement rejection is improper.

1. Breadth of the Claimed Genus Does Not Equal Non-enablement

The Examiner contends that the genus of water-soluble complexing agents is "extremely broad and encompasses an extremely large class of agents." Action, page 6. "Given its broadest reasonable interpretation," the Examiner continues, "any water-soluble complexing agent, admixed with a drug, would read on Applicants' instantly claimed mixture." *Id.* The Examiner

LAW OFFICES OF
CHRISTENSEN O'CONNOR JOHNSON KINDNESS PLLC
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

concludes that this alleged breadth would necessitate undue experimentation "in order to develop an effective method for producing a drug/carrier solid dispersion using the instantly claimed method without guidance from the prior art." *Id.*

Applicants disagree with the rejection, as the Examiner has failed provide acceptable evidence or reasoning to support the contention that the alleged breadth of the claimed genus corresponds to undue experimentation in the context of the claimed methods. *See Ex parte Cho*, Appeal No. 2001-2646 at page 9 (Bd. Pat. App. & Interf. 2003), citing *In re Marzocchi*, 439 F.2d 220, 224 (CCPA 1971) ("It is incumbent upon the Patent Office, whenever a[n enablement] rejection ... is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning ..."). As emphasized on page 8 of *Cho* in the context of an accusation regarding allegedly over-broad claims in that case, an "examiner must do more than point to a lack of evidence supporting the breadth of the claims. The burden is not on the applicants to show that the disclosure in the specification is correct; the burden is on the examiner to show that it is not." Here, the Examiner fails to provide specific evidence or reasoning to show that methods set forth in the application could not be applied to any member of the claimed genus. For example, there is no reasoning to show that the methods set forth in the Examples cannot be practiced with any water-soluble complexing agent. To the extent that the Examiner bases the rejection on an alleged lack of further evidence of enablement, the Board in *Cho* stated that "[p]ointing out a lack of independent evidentiary support is not enough" to carry the burden of establishing a *prima facie* case of non-enablement. *Id.* at page 9.

2. The Specification, Combined with the Knowledge of a Skilled Artisan, Provides Sufficient Guidance to Enable the Claimed Genus

The Manual of Patent Examining Procedure states that "[t]he test for enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in

the patent coupled with information known in the art without undue experimentation." M.P.E.P. § 2164.01 (*quoting United States v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988)). Despite applicants' lack of burden to show that the specification is correct, as noted above, applicants provide the following argument to show that the specification, in combination with the knowledge available to a skilled artisan, enables the claimed genus of "water-soluble complexing agents."

The term "soluble" is defined in the specification at page 5: "the terms 'soluble/insoluble' are meant with respect to water at room temperature (20°C)." The specification also states that, "[t]he organic carriers used in the present invention are preferably characterized by non high surface area, for example, between 0.05 and 20 m^2/g." *Id.* As recited by Claim 1 and noted in the specification, organic carriers may be selected from the group consisting of water-soluble complexing agents, water-insoluble cross-linked polymers, and mixtures thereof. See Specification, page 4. As acknowledged by the Examiner, the specification also describes examples of such water-soluble complexing agents. Specification, page 5. In addition to the description of how to carry out methods of the claimed invention as explained on pages 4-9 of the specification, working examples that employ β-cyclodextrine are also provided. This collective guidance therefore not only provides a skilled artisan with quantitative parameters as to what qualifies as a water-soluble complexing agent, but also provides examples of the genus and how they may be used. From this information, a skilled artisan would be able to deduce which agents qualify as water-soluble complexing agents and would be able to employ such agents in the claimed methods without undue experimentation.

3. No Evidence or Reasoning Suggests that the Claimed Genus Suffers from Unpredictability

The amount of guidance or direction needed to enable an invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *See*

LAW OFFICES OF
CHRISTENSEN O'CONNOR JOHNSON KINDNESS PLLC
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

M.P.E.P. § 2164.03; *see also In re Fisher*, 427 F.2d 833, 839 (CCPA 1970). The Examiner has provided no evidence or reasoning to show that the state of the art regarding water-soluble complex agents is unpredictable or that any aspect of their use in the claimed invention is unpredictable. As such, there is no legal basis to conclude that the guidance provided in the specification, discussed above, is insufficient to enable the claimed invention. Indeed, water-soluble complexing agents have been studied for many years: for example, cyclodextrins were discussed as complexing agents in U.S. Patent No. 5,362,758, which issued November 8, 1994 (Appendix 1).

4. Conclusion

The foregoing demonstrates that not only has the specification provided sufficient guidance to a skilled artisan as to how to practice the claimed invention, but that the Examiner has failed to carry his burden to show that the invention is not enabled. Applicants therefore respectfully request withdrawal of the enablement rejection.

IV. The Indefiniteness Rejection of Claim 1 Is Overcome

Claim 1 is rejected under 35 U.S.C. § 112, second paragraph, as indefinite. In particular, the Examiner contends that the terms "particulate organic carrier" and "a composite containing the drug dispersed within the particulate organic carrier deposited both on the surfaces and inside the organic carrier particles" are each unclear. Applicants respectfully disagree.

The term "particulate organic carrier" as recited in Claim 1 is clear. For example, *Hawley's Condensed Chemical Dictionary* of 2001 (Appendix 2) provides the following definition of this term: "Solid or liquid matter that is dispersed in a gas, or insoluble solid matter dispersed in a liquid, that gives a heterogeneous mixture." Citing *Vitrionics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1584, n. 6 (Fed. Cir. 1996), the Federal Circuit in *Phillips v. AWH Corp.*, 415 F.3d 1303, 1322 (Fed. Cir. 2005) stated that dictionaries may be consulted to

LAW OFFICES OF
CHRISTENSEN O'CONNOR JOHNSON KINDNESS PLLC
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

understand the technology of a claim and to construe claim terms as long as the definition does not contradict any definition found in or ascertained by the intrinsic documents. The recitation in Claim 1 of "a particulate organic carrier selected from the group consisting of water-soluble complexing agents, water-insoluble cross-linked polymers, and mixtures thereof" is not inconsistent with the definition found in Appendix 2. Properties and examples of organic carriers provided in the specification, such as pages 4-5, are also not inconsistent with this definition. The teachings of the specification are also not inconsistent with the definition offered by the Examiner at page 7 of the Action: "Broadly interpreted, a carrier in particulate form may comprise a sprayed liquid carrier or a solid granular particulate form." The foregoing demonstrates that the term "particulate organic carrier" would be understood by a person of skill in the art. *See* M.P.E.P. § 2173.02 (claims are to be read in view of the specification, the prior art, and the interpretation given to the claim by one of ordinary skill in the art). Applicants therefore request withdrawal of the indefiniteness rejection regarding this term.

With respect to the contested phrase, "a composite containing the drug dispersed within the particulate organic carrier deposited both on the surfaces and inside the organic carrier particles," applicants note that Claim 1 has been amended to remove this phrase and instead read, "wherein the drug is dispersed inside of the organic carrier particles as well as on the external surface of the particles." Support for this amendment may be found in the specification as originally filed. *See,* e.g., pages 3 and 4. Applicants submit that amended Claim 1 is clear, and request reconsideration and withdrawal of the indefiniteness rejection.

V. The Obviousness Rejections Are Overcome

Three sets of claims are rejected under 35 U.S.C. § 103(a) as obvious over three different sets of references. Each rejection relies, in whole or in part, on the teachings of Miyamoto et al. (U.S. Patent No. 6,462,093) ("Miyamoto"). However, each of the obviousness rejections is

LAW OFFICES OF
CHRISTENSEN O'CONNOR JOHNSON KINDNESS PLLC
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

improper because, at a minimum, this reference, alone or in combination, fails to teach every limitation of the claimed invention. In addition, not only is the motivation cited by the Examiner to combine references with Miyamoto insufficient to establish a *prima facie* case of obviousness, but the Examiner relies upon conclusory reasoning to assert that a combination of Miyamoto with other cited art has a reasonable expectation of success. Applicants therefore respectfully disagree with each of the rejections.

Below, applicants first demonstrate that Claims 1-3, 8, and 10 are patentable. Because the remaining rejections are drawn to claims that depend from independent Claim 1, these rejections should also be withdrawn because Claim 1 is patentable.

1. Claims 1-3, 8, and 10 Are Patentable Over Aoki and Miyamoto

Claims 1-3, 8, and 10 are rejected as obvious over the combined teachings of Aoki (EP Patent No. 1 308 156) and Miyamoto. The Examiner contends that Aoki teaches each aspect of Claim 1 except that it does not teach that the temperature achieved during microwave irradiation "is above the melting point of the slightly soluble medicament, nor is it taught that microwaving occurs for longer than four minutes." Action, page 10. Miyamoto is said to account for these deficiencies in its teaching of adding an amorphous state-inducing agent (e.g., succinic acid) to a formulation taught by Aoki, thereby depressing the melting point temperature of the medicament and increasing the period of microwave exposure time. The Examiner's asserted motivation to combine these references follows the same reasoning, in that Miyamoto's teaching that addition of the agent lowers the melting temperature of the medicament and enables the mixture to be exposed to higher wattages of microwave irradiation for longer periods of time. The Examiner also asserts that the combination of Aoki and Miyamoto would have a reasonable expectation of success.

LAW OFFICES OF
CHRISTENSEN O'CONNOR JOHNSON KINDNESS PLLC
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

Applicants respectfully disagree. *KSR Int'l Co. v. Teleflex* confirmed that the Graham Factor Analyses should be used in determining whether a claimed invention is obvious under 35 U.S.C. § 103(a). 127 S. Ct. at 1727, 1739 (2007). Therefore, the following subsections set forth the (1) rejected claims; (2) scope and content of the cited art, and the differences between the rejected claims and the cited art; and (3) an explanation as to why these differences are not rendered obvious by these references. In particular, this explanation demonstrates that there has been no showing of "an apparent reason to combine the known elements in the fashion claimed by the patent at issue." *Id.* at 1741. Each of the rejections is therefore improper.

A. The Rejected Claims

Amended Claim 1 is drawn to a process for the preparation of a composite containing a drug dispersed in a particulate organic carrier, comprising: a) mixing a drug and a particulate organic carrier selected from the group consisting of water-soluble complexing agents, water-insoluble cross-linked polymers, and mixtures thereof; and b) applying an oscillating electromagnetic field to the mixture, wherein the oscillating electromagnetic field is microwave irradiation modulated to increase the temperature of the mixture to a temperature greater than the melting temperature of the drug and maintained at the temperature greater than the melting temperature of the drug for at least 5 minutes to provide a composite containing the drug, wherein the drug is dispersed inside of the organic carrier particles as well as on the external surface of the particles, wherein the drug is present in the composite in amorphous form in a quantity greater than or equal to 50% by weight based on the total amount of the drug. Claims 2, 3, 8, and 10 depend from this claim.

B. Scope and Content of the Cited Art, and Differences between the Cited Art and the Rejected Claims

Aoki describes a solid dispersion composition comprising a slightly soluble medicament and having an improved solubility, and methods of making this composition. Aoki, para. [0007].

LAW OFFICES OF
CHRISTENSEN O'CONNOR JOHNSON KINDNESS PLLC
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

The medicament is blended with a water-soluble polymer and exposed to microwaves. *Id.* at para. [0008]. While Aoki suggests that microwave irradiation may last longer than 2.5 minutes (para. [0035]), each of the Examples describes irradiation lasting up to only 4 minutes. A medicament may be nifedipine. *Id.*

Miyamoto describes a process for producing a solid dispersion of a sparingly water-soluble medical substance comprising subjecting the substance, an amorphous state-inducing agent, and an amorphous state-stabilizing agent to heat treatment or mechanochemical treatment. Miyamoto, Abstract. Miyamoto also instructs that when employing high-frequency heating, such as microwave heating, "the sparing water-soluble medical substance can be converted to the amorphous state by heating the mixture of the sparingly water-soluble medical substance and the amorphous state-stabilizing agent ... without using the amorphous state-inducing agent." Col 4, lines 44-49. *See also*, Abstract. The Abstract also states that "[t]hese processes make it possible to make sparingly water-soluble medical substance[s] amorphous at a temperature lower than those employed in the conventional methods."

Miyamoto further instructs that an amorphous state-inducing agent, such as succinic acid, is one that is capable of depressing the melting point of the mixture of it with a medical substance. *Id.* at Col. 3, lines 23-56. It is preferable to depress the melting point of the mixture to 5°C, 15°C, or, more particularly, 25°C or more as compared to the melting point of the medicament. *Id.* at Col. 4, lines 31-43. Heating is applied at the amorphous state-induction temperature. *Id.* at Col. 7, lines 16-19. Microwave heating is taught at, e.g., Col. 7, lines 34-45, as well as the use of oscillation energy (Col. 7, lines 11-15). Treatment time ranges generally from 20 to 120 minutes, but 3 to 40 minutes when employing batch heating. Col. 7 at lines 16-25 and 62-63.

LAW OFFICES OF
CHRISTENSEN O'CONNOR JOHNSON KINDNESS[PLLC]
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

Neither of these references describe "microwave irradiation modulated to increase the temperature of the mixture to a temperature greater than the melting temperature of the drug and maintained at the temperature greater than the melting temperature of the drug for at least 5 minutes" as presently claimed. In addition, neither reference describes production of a "composite containing the drug, wherein the drug is dispersed inside of the organic carrier particles as well as on the external surface of the particles" as presently claimed.

C. The Differences between the Cited Art and the Rejected Claims Are Not Obvious Differences

In the context of an obviousness rejection, the Supreme Court explained the importance of "identify[ing] a reason" why a skilled artisan would be prompted to arrive at the presently claimed invention. *KSR*, 127 S. Ct. at 1727. The Court noted that there should be an "explicit" analysis regarding "whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue." *Id.* Here, no such reason exists as every claimed element is not taught or suggested in the cited art such that even if the references were combined, one would not arrive at the claimed invention. Moreover, the Examiner's asserted motivation to combine the references does not result in the claimed method, and at least one cited reference actually teaches away from the claimed method. Finally, the Examiner provides no explicit analysis as to why the combination of references would be successful. Indeed, the present specification provides evidence to the contrary.

1. All elements of the claimed invention are not taught by the cited art

Citing the *KSR* decision, Section 2143.02 of the M.P.E.P. states, "A rationale to support a conclusion that a claim would have been obvious is that ***all the claimed elements were known in the prior art***...." (emphasis added) (internal citation omitted). However, no evidence or reasoning has been presented to show that each element of Claim 1 is known in the art. *See*

LAW OFFICES OF
CHRISTENSEN O'CONNOR JOHNSON KINDNESS PLLC
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

M.P.E.P. § 2142 ("The Examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness."). This deficiency alone warrants withdrawal of the rejection.

In particular, Claim 1 recites that microwave irradiation of the mixture is modulated to "increase the temperature of the mixture to a temperature greater than the melting temperature of the drug and maintained at the temperature greater than the melting temperature of the drug for at least 5 minutes." The cited references neither teach nor suggest subjecting mixtures to a temperature greater than the melting temperature of the drug and maintenance of that temperature for greater than 5 minutes. The Examiner provides no evidence or reasoning to show that mixtures taught by the cited art are heated to a temperature above the melting temperature of the drug, or that the temperature is maintained for at least 5 minutes. Indeed, the Examiner concedes that Aoki does not teach that the temperature achieved during microwave irradiation is greater than the melting temperature of the drug in the mixture (Action, p 10). Further, Miyamoto emphasizes that its mixtures are heated to the amorphous-state induction temperature, which is lower than the melting temperature of the drug in the mixture.

In addition, neither reference describes production of a "composite containing the drug, wherein the drug is dispersed inside of the organic carrier particles as well as on the external surface of the particles" as presently claimed. The Examiner's rejection does not mention this claimed element or how it is obvious over the cited art. This is a second shortcoming associated with the rejection.

Because a *prima facie* case of obviousness has not been factually supported, the rejection cannot stand. For at least this reason, applicants respectfully request its withdrawal.

2. The alleged motivation to combine the references does not produce the claimed method and actually teaches away from it

Regarding an alleged motivation to combine the teachings of Aoki and Miyamoto, the Examiner contends that it would have been obvious "to have devised the instantly claimed

LAW OFFICES OF
CHRISTENSEN O'CONNOR JOHNSON KINDNESS PLLC
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

method and achieved the resulting composition by adding an agent such as succinic acid (e.g.[,] an amorphous state-inducing agent) to the formulation of Aoki and increasing the period of microwave exposure time." Action, page 11 (emphasis added). This reasoning does not support an obviousness rejection because in Miyamoto, the amorphous-state inducing agent permits melting of the mixture at the amorphous state-induction temperature, which is lower than the melting temperature of the drug, to provide the dispersions taught therein. Indeed, Miyamoto states at Col. 6, lines 40-43: "In this occasion, the mixture is preferably heated at the temperature not more than the melting point of the sparingly water-soluble medical substance." As noted above, Aoki does not teach exposing a mixture to temperatures greater than the melting temperature of the drug. By contrast, the claimed invention is drawn to using oscillating microwave irradiation to facilitate increasing of the temperature of the mixture to one that is greater than the melting temperature of the drug. In view of the purpose associated with an amorphous state-inducing agent, an artisan would not be motivated to use such an agent to arrive at the presently claimed invention.

Moreover, even if an amorphous-state inducing agent is not employed in the methods of Miyamoto, such as when microwave radiation is employed, Miyamoto still instructs that a mixture of the drug and the amorphous-state stabilizing agent is heated to a temperature that is lower than temperatures used in conventional methods. Nowhere does Miyamoto suggest that this translates to heating a mixture to a temperature that is greater than that of the melting point of the drug in the mixture, much less maintenance of that temperature for at least 5 minutes. Indeed, the conventional methods discussed in the "Background Art" section of Miyamoto refer to methods that heat mixtures at temperatures lower than the melting temperature of the drug in the mixture. *See*, e.g., Col. 1, lines 55-62; and Col. 2, lines 1-5.

LAW OFFICES OF
CHRISTENSEN O'CONNOR JOHNSON KINDNESS[PLLC]
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

Not only does Miyamoto not teach the claimed method with respect to the temperature the mixture is heated to, but this reference actually teaches away from the claimed method in that it instructs a heating temperature of a mixture that is lower than the melting temperature of the drug, and/or lower than the temperature used in conventional methods. That a reference teaches away is sufficient on its own to defeat a *prima facie* case of obviousness. *See Winner Int'l. Royalty Corp. v. Wang*, 202 F.3d 1340, 1349-50 (Fed. Cir. 2000).

The foregoing demonstrates that the alleged motivation to combine the references is factually unsupported. This presents a second reason why applicants request withdrawal of the obviousness rejection.

3. The Examiner's reasoning is conclusory regarding a reasonable expectation of success in combining the cited art

Citing *KSR*, the M.P.E.P. notes that "rejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." M.P.E.P. § 2143.01 (citing *KSR*, 127 S. Ct. at 1741) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)). However, in stating that a combination of Aoki and Miyamoto would be reasonably successful, the Examiner relies upon such improper conclusory statements.

A reasonable expectation of success is required when an obviousness rejection is based on the modification or combination of cited art. M.P.E.P. § 2143.02. The entirety of the Examiner's reasoning regarding a reasonable expectation of success is as follows: "Based on the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention." Action, page 11. This statement does not amount to the factual support demanded by M.P.E.P. § 2142, noted above, with respect to the burden an examiner carries to establish a *prima facie* case of obviousness.

LAW OFFICES OF
CHRISTENSEN O'CONNOR JOHNSON KINDNESS PLLC
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

Moreover, reference Examples 5 and 6 of the present specification describes methods and results obtained when using teachings of the Aoki and Miyamoto references, respectfully. Each of these Examples show that these methods resulted in low conversion of the drug into amorphous form (Example 5), or carbonization of the mixture (Example 6). In view of these comparative examples that tested the conditions of Aoki and Miyamoto separately, it is difficult to see how a skilled artisan would presume that a combination of these references would have a reasonable expectation of success.

4. Conclusion

Because the cited art fails to teach every element of the claimed invention, and because the alleged motivation to combine the cited art cannot result in the claimed invention and does not show a reasonable expectation of success, the obviousness rejection is improper and should be withdrawn.

2. Claims 4, 5, 9, and 21 Are Patentable Over Miyamoto

Claims 4, 5, 9, and 21, which depend from Claim 1, are rejected as obvious over Miyamoto. Applicants respectfully disagree. As discussed above with respect to Claim 1, this reference fails to teach every element of the claimed invention; as such, there is no "apparent reason" why a skilled artisan would look to this reference to arrive at subject matter of the rejected claims. *KSR*, 127 S. Ct. at 1741. Thus, as with Claim 1, these dependent claims are also not obvious over the art. Applicants therefore respectfully request withdrawal of the rejection.

3. Claims 5 and 6 Are Patentable Over Miyamoto, Aoki, and Lautenschläger

Claims 5 and 6, which depend from Claim 1, are rejected as obvious over Miyamoto, Aoki, and Lautenschläger (U.S. Patent No. 5,447,077). Applicants respectfully disagree. As discussed above, Miyamoto and Aoki, either separately or together, fail to teach or suggest every element of the claimed invention. Further, no motivation exists to combine these references and

LAW OFFICES OF
CHRISTENSEN O'CONNOR JOHNSON KINDNESS PLLC
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

there is no reasonable expectation of success to achieve the claimed method with respect to such a combination. Lautenschläger fails to account for these deficiencies, as this reference is directed towards devices for evaporation treatment of a sample material in a container. Lautenschläger, Abstract. Because these dependent claims are not obvious over the art, applicants respectfully request withdrawal of this rejection.

CONCLUSION

In view of the above amendments and foregoing remarks, applicants believe that Claims 1-10 and 21 are in condition for allowance. If any issues remain that may be expeditiously addressed in a telephone interview, the Examiner is encouraged to telephone applicants' attorney at 206.695.1649.

Respectfully submitted,

CHRISTENSEN O'CONNOR
JOHNSON KINDNESS[PLLC]

Tamara Kale

Tamara A. Kale, Ph.D.
Registration No. 53,087
Direct Dial No. 206.695.1649

TAK:aew

LAW OFFICES OF
CHRISTENSEN O'CONNOR JOHNSON KINDNESS[PLLC]
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

Appendix 1

US005362758A

United States Patent [19]

Ahmed

[11] Patent Number: 5,362,758

[45] Date of Patent: Nov. 8, 1994

[54] **OPHTHALMIC PIROXICAM SOLUTION**

[75] Inventor: **Imran Ahmed**, New York, N.Y.

[73] Assignee: **Pfizer Inc.**, New York, N.Y.

[21] Appl. No.: **970,350**

[22] Filed: **Oct. 30, 1992**

Related U.S. Application Data

[63] Continuation of Ser. No. 584,227, Sep. 18, 1992, abandoned.

[51] **Int. Cl.**[5] **A61K 31/74**

[52] **U.S. Cl.** **514/777**; 514/781; 514/912; 514/914; 514/915; 424/427; 424/48

[58] **Field of Search** 424/427, 428, 78.04; 514/912, 914, 915, 777, 781

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,591,584	7/1971	Lombardino	260/243
4,470,965	9/1984	Wolf et al.	514/597
4,474,811	10/1984	Masuda et al.	514/570
4,678,666	7/1986	Nozawa et al.	424/81
4,688,053	12/1986	Fries	514/222

FOREIGN PATENT DOCUMENTS

899587	8/1984	Belgium .
0336200	3/1989	European Pat. Off. .
62-142116	6/1987	Japan .

Primary Examiner—Thurman K. Page
Assistant Examiner—C. Azpuru
Attorney, Agent, or Firm—Peter C. Richardson; Paul H. Ginsburg; Seymour G. Bekelnitzky

[57] **ABSTRACT**

Aqueous solutions for treating inflammations of the eye, comprising: from about 0.03–3 weight percent of piroxicam; an effective amount of a buffer; from about 0 to about 1 weight percent of a wetting agent; from about 0 to about 5 weight percent of a pH adjusting agent; from about 0 to about 5 weight percent of a tonicity agent; an effective amount of a preservative; from about 0 to about 3 weight percent of a demulcent polymer; from about 0 to about 40 weight percent of a complexing agent; and from about 0 to about 0.1 weight percent of a stabilizer; and having a pH between about 7 and about 10.

14 Claims, No Drawings

OPHTHALMIC PIROXICAM SOLUTION

This is a continuation, of application Ser. No. 07/584,227, filed on Sep. 18, 1992 now abandoned.

BACKGROUND OF THE INVENTION

This invention relates to aqueous piroxicam solutions useful in the treatment of inflammations of the eye such as allergic conjunctivitis, edemas, acute uveitis, ocular trauma, scleritis and keratoconjunctivitis.

Piroxicam, the chemical name of which is N-(2-pyridyl)-2-methyl-4-hydroxy-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide, is a nonsteroidal anti-inflammatory agent. It is described and claimed in U.S. Pat. No. 3,591,584.

Several piroxicam containing pharmaceutical compositions for uses other than ophthalmic administration are known. U.S. Pat. No. 4,688,053 refers to injectable solutions containing piroxicam. U.S. Pat. No. 4,678,666 refers to piroxicam containing gels for dermatological administration. Japanese Patent Application Disclosure 62-142116 refers to piroxicam containing suppositories.

Aqueous piroxicam suspensions for ophthalmic use are also known. Belgian patent 899,587 refers to an anti-inflammatory eye lotion that is a suspension of piroxicam in an aqueous, sterile, hypertonic solution.

In the ophthalmic compositions of the present invention, piroxicam, the active ingredient, is dissolved in an aqueous solution, facilitating administration of the drug, accuracy in dosing and patient toleration. The fact that the active ingredient is dissolved in solution also prevents blurring and causes such compositions to be faster acting than suspensions of piroxicam.

The aqueous piroxicam solutions of the present invention also exhibit substantially greater stability than the aqueous piroxicam suspensions. They need not be nitrogen purged during preparation and storage. The stability inherent in the novel solutions of this invention may be further enhanced by packaging them in containers capable of blocking transmission of light having a wavelength in the range from about 290 nm to about 550 nm.

SUMMARY OF THE INVENTION

The present invention relates to aqueous solutions for treating inflammations of the eye comprising: from about 0.03 to about 3 weight percent of piroxicam; an effective amount of a buffer; from about 0 to about 1 weight percent of a wetting agent; from about 0 to about 5 weight percent of a pH adjusting agent; from about 0 to about 5 weight percent of a tonicity agent; an effective amount of a preservative; from about 0 to about 3 weight percent of a demulcent polymer; from about 0 to about 40 weight percent of a complexing agent; and from about 0 to about 0.1 weight percent of a stabilizer; and having a pH between about 7 and about 10. These solutions are hereinafter referred to as solutions having Formulation I. The solutions having Formulation I are useful in the treatment of inflammations of the eye such as allergic conjunctivitis, edemas, acute uveitis, ocular trauma, scleritis and keratoconjunctivitis.

The present invention also relates to a method of treating inflammatory diseases of the eye such as allergic conjunctivitis, edemas, acute uveitis, ocular trauma, scleritis and keratoconjunctivitis in a mammal, including a human, comprising administering to a mammal in need of such treatment an anti-inflammatory effective amount of a solution having Formulation I.

The present invention also relates to a container comprising a packaging material capable of blocking the transmission of light having a wavelength from about 290 nanometers to about 550 nanometers, said container having therein a solution having Formulation I.

DETAILED DESCRIPTION OF THE INVENTION

In a preferred embodiment of this invention, the solution having Formulation I is an aqueous isotonic solution comprising: from about 0.03 to about 3 weight percent piroxicam; from about 0.5 to about 1 weight percent boric acid; from about 0.5 to about 1 weight percent sodium borate decahydrate; from about 0.4 to about 1 weight percent glycerin; from about 0.04 to about 1 weight percent polyethylene glycol 300 (PEG 300); from about 0.004 to about 0.01 weight percent thimerosal; and from about 0.03 to about 0.3 weight percent sodium hydroxide.

In a more preferred embodiment of this invention, the solution having Formulation I is an isotonic aqueous solution comprising: about 0.3 weight percent piroxicam; about 0.67 weight percent boric acid; about 0.21 weight percent sodium borate decahydrate; about 1.0 weight percent glycerin; about 1.0 weight percent PEG 300; about 0.004 weight percent thimerosal; and about 0.11 weight percent sodium hydroxide.

Wetting agents, demulcent polymers, and complexing agents may be optionally added to the solutions having Formulation I without compromising efficacy or stability.

Buffers that may be employed in the present invention include: boric acid and borate salts such as sodium borate; carbonate salts such as sodium carbonate and potassium carbonate. Boric acid/sodium borate decahydrate is preferred. An effective amount of a buffer is generally from about 0.05 weight percent to about 10 weight percent.

Tonicity agents that may be employed in the present invention include propylene glycol, PEG 300, polyethylene glycol 400 (PEG 400), glycerin, polysorbate, sorbitol, dextran 40 and dextran 70. Preferably the tonicity agent comprises one or both of PEG 300 and glycerin.

Examples of preservatives that may be employed include thimerosal, phenylmercuric acetate and phenylmercuric nitrate, with thimerosal being preferred. An effective amount of a preservative is generally from about 0.001 weight percent to about 0.75 weight percent.

Demulcent polymers may optionally be added to the solutions of Formulation I. Because of their ability to hold large amounts of water, they are useful for coating and thus moisturizing the cornea of the eye. Cellulose derivatives, Dextran 40, Dextran 70, gelatin and liquid polyols are among the demulcent polymers suitable for use with this invention.

Wetting agents such as polysorbates, poloxamer, tyloxapol and lecithin may also optionally be added to the solutions of Formulation I to optimally wet the surface of the eye.

The solutions having Formulation I have a pH of between about 7 and about 10. To maintain the pH of these solutions, pH adjusting agents may be added. Examples of suitable pH adjusting agents include: a) mineral acids such as sulfuric acid, nitric acid and phos-

phoric acid; b) alkali salts such as sodium and potassium hydroxide; and c) organic acids such as acetic and citric acids.

Complexing agents may also optionally be added to solutions having Formulation I to facilitate the dissolution of greater amounts of piroxicam. These are especially useful in solutions having a piroxicam concentration greater than 0.3 weight percent. Cyclodextrins and soluble cyclodextrin derivatives may be used for this purpose.

The water used in solutions having Formulation I is generally sterilized, and is peferably distilled and deionized.

The stability of the solutions having Formulation I is enhanced by storing them in a container comprising a packaging material that is capable of blocking the transmission of light having a wavelength from about 290 nanometers to about 550 nanometers. In a preferred embodiment of this invention, a solution having Formulation I is stored in an opaque low density polyethylene bottle having low density polyethylene dropper tips and a polypropylene cap.

The ophthalmic piroxicam solutions of the present invention are administered topically by applying them to the cul-de-sac of the eye from a dropper controlled bottle or dispenser. A typical dose regimen for an adult human may range from about 2 to about 8 drops per day (about 0.3 mg to about 1.2 mg piroxicam for a 0.3 weight percent piroxicam solution). Dosages for adult humans may, however, be as high as about 20 mg piroxicam per day (133 drops per day).

The following examples illustrate but do not limit the scope of this invention.

EXAMPLE 1

A 0.03 weight percent ophthalmic piroxicam solution was prepared by dissolving 67.0 g (0.67 weight percent) boric acid, 20.7 g (0,207 weight percent) sodium borate decahydrate, 100.0 g (1.0 weight percent) glycerin, 100.0 g of polyethylene glycol 300 (1.0 weight percent), and 0.40 g (0.004 weight percent) thimerosal into approximately 8000 g of deionized, distilled water. The pH of the solution was brought to 7.9 by the addition of an appropriate amount of an 8 weight percent stock solution of sodium hydroxide. Piroxicam, 3.0 g, was dissolved into the above vehicle with agitation. The vehicle pH was re-adjusted to pH 7.9 by the addition of an 8 weight percent stock solution of sodium hydroxide. A total of approximately 5 g of sodium hydroxide was required to adjust the pH, resulting in a concentration of 0.05 weight percent sodium hydroxide in the formulation. The final batch weight was brought to 10,000 g with the addition of the required amount of water. This formulation was then passed through a 0.2 micron sterilizing filter, and held there for filling.

EXAMPLE 2

A 0.10 weight percent ophthalmic piroxicam solution was prepared by dissolving 67.0 g (0.67 weight percent) boric acid, 20.7 g (0.207 weight percent) sodium borate decahydrate, 100.0 g (1.0 weight percent) glycerin, 100.0 g of polyethylene glycol 300 (1.0 weight percent), and 0.40 g (0.004 weight percent) thimerosal into approximately 8000 g of deionized, distilled water. The pH of the solution was brought to 8.2 by the addition of an appropriate amount of an 8 weight percent stock solution of sodium hydroxide. Piroxicam, 10.0 g, was dissolved into the above vehicle with agitation. The vehicle pH was re-adjusted to pH 8.2 by the addition of an 8 weight percent stock solution of sodium hydroxide. A total of approximately 8 g of sodium hydroxide was required to adjust the pH, resulting in a concentration sodium hydroxide in the formulation. The final batch weight was brought to 10,000 g with the addition of the required amount of water. This formulation was passed through a 0.2 micron sterilizing filter, and held there for filling.

EXAMPLE 3

A 0.30 weight percent ophthalmic piroxicam solution was prepared by dissolving 67.0 g (0.67 weight percent) boric acid, 20.7 g (0.207 weight percent) sodium borate decahydrate, 100.0 g (1.0 weight percent) glycerin, 100.0 g of polyethylene glycol 300 (1.0 weight percent), and 0.40 g (0.004 weight percent) thimerosal into approximately 8000 g of deionized, distilled water. The pH of the solution was brought to 8.6 by the addition of an appropriate amount of an 8 weight percent stock solution of sodium hydroxide. Piroxicam, 30.0 g, was dissolved into the above vehicle with agitation. The vehicle pH was re-adjusted to pH 8.6 by the addition of an 8 weight percent stock solution of sodium hydroxide. A total of approximately 21 g of sodium hydroxide was required to adjust the pH, resulting in a concentration of 0.21 weight percent sodium hydroxide in the formulation. The final batch weight was brought to 10,000 g with the addition of the required amount of water. This formulation was passed through a 0.2 micron sterilizing filter, and held for filling.

EXAMPLE 4

The following package was used to contain the solution of Example 1.

Component	Description
Amber bottle	Low density polyethylene with a metallic oxide brown color concentrate and a tinuvin ultraviolet (UV) inhibitor
Dropper tips	White low density polyethylene
Cap	White polypropylene with a zinc sulfide color concentrate and a UV inhibitor

I claim:

1. An aqueous solution for treating inflammations of the eye comprising: from about 0.03–3 weight percent of piroxicam; a buffer comprising from about 0.5 to about 1 percent by weight of boric acid and from about 0.5 to about 1 percent by weight of sodium borate; from about 0 to about 1 weight percent of a wetting agent; from about 0 to about 5 weight percent of a pH adjusting agent; from about 0 to about 5 weight percent of a tonicity agent; an effective amount of a preservative; from about 0 to about 3 weight percent of a demulcent polymer; from about 0 to about 40 weight percent of a complexing agent; and from about 0 to about 0.1 weight percent of a stabilizer; and having a pH between about 7 and about 10.

2. A solution according to claim **1**, wherein the preservative is selected from the group consisting of thimerosal, phenyl mercuric acetate and phenyl mercuric nitrate.

3. A solution according to claim 1, comprising from about 0.4 to about 1 weight percent glycerin; from about 0.04 to about 1 weight percent polyethylene glycol 300; from about 0.4 to about 1 weight percent thimerosal; and from about 0.03 to about 0.3 weight percent sodium hydroxide.

4. A solution according to claim 1, comprising: about 0.3 weight percent piroxicam; about 0.67 weight percent boric acid; about 0.21 weight percent sodium borate decahydrate; about 1.0 weight percent glycerin; about 1.0 weight percent polyethylene glycol 300; about 0.004 weight percent thimerosal; and about 0.11 weight percent sodium hydroxide.

5. A solution according to claim 1, wherein said solution comprises about 3 grams piroxicam, about 60 grams boric acid, about 21 grams sodium borate, about 100 grams glycerin and about 100 grams PEG 300, and wherein said solution has a pH of about 8 and the total weight of the solution is about 10,000 grams.

6. A solution according to claim 1, wherein the wetting agent is selected from the group consisting of polysorbates poloxamer, tyloxapol and lecithin.

7. A solution according to claim 1, wherein the tonicity agent is selected from the group consisting of glycerin, polyethylene glycol 300, propylene glycol, polyethylene glycol 400, polysorbate, Dextran 40 and dextran 70 and mixture thereof.

8. A solution according to claim 2, wherein the preservative is thimerosal.

9. A solution according to claim 1, wherein the demulcent polymer is selected from the group consisting of cellulose, dextran 40, dextran 70, gelatin and liquid polyols.

10. A solution according to claim 1, wherein the complexing agent is cyclodextrin.

11. A solution according to claim 1, wherein the stabilizer is selected from sodium EDTA and sodium bisulfite.

12. A solution according to claim 1, wherein the pH adjusting agent is selected from organic acids, mineral acids and alkali bases.

13. A method of treating an inflammation of the eye in a mammal, comprising administering to a mammal in need of such treatment an anti-inflammatory effective amount of a solution according to claim 1.

14. A solution according to claim 1, wherein the tonicity agent is a mixture of glycerin and a poly(ethylene glycol).

* * * * *

Appendix 2

Hawley's

Condensed Chemical Dictionary

Fourteenth Edition

Revised by

Richard J. Lewis, Sr.

JOHN WILEY & SONS, INC.

This book is printed on acid-free paper. ∞

Published simultaneously in Canada.

For ordering and customer service, call 1-800-CALL-WILEY.

Library of Congress Cataloging-in-Publication Data:

Condensed chemical dictionary.
Hawley's condensed chemical dictionary.—14th ed./ rev. by Richard J. Lewis, Sr. p. cm.
Includes index.
ISBN 0-471-38735-5 (cloth: acid-free paper)
1. Chemistry—Dictionaries. I. Title: Condensed chemical dictionary. II Hawley, Gessner Goodrich, 1905– III. Lewis, Richard J., Sr. IV. Title.

QD5 C5 2002
540″.3--dc21

2001045614

Printed in the United States of America.

10 9 8 7 6 5 4 3 2 1

parison. (1) An unformed mass of molten glass from which finished products are manufactured. (2) An extruded tube of plastic from which toys and similar items are made by blow molding.

Paris white. See whiting.

Parkes process. A standard process for the separation of silver from lead. From 1 to 2% molten zinc is added to the lead-silver mixture, heated to above the melting point of zinc. A scum containing most of the silver and zinc forms on the surface; this is separated and the silver recovered. The separation of silver is not complete, and the process is repeated several times.

paromomycin sulfate. $C_{23}H_{47}N_5O_{18}S$. Antibiotic from a strain of *Streptomyces*.
Properties: Creamy white powder; odorless; hygroscopic. Soluble in water; insoluble in chloroform and ether.
Grade: ND.
Use: Medicine (antimicrobial).

partial pressure. The pressure due to one of the several components of a gaseous or vapor mixture. In general this pressure cannot be measured directly but is obtained by analysis of the gas or vapor and calculated by use of Dalton's law.
See Raoult's law.

particle. Any discrete unit of material structure; the particulate basis of matter is a fundamental concept of science. The size ranges of particles may be summarized as follows: (1) Subatomic: protons, neutrons, electrons, deuterons, etc. These are collectively called fundamental particles. (2) Molecular: includes atoms and molecules with size ranging from a few angstroms to half a micron. (3) Colloidal: includes macromolecules, micelles, and ultrafine particles such as carbon black, resolved via electron microscope, with size ranges from 1 millimicron up to lower limit of the optical microscope (1 micron). (4) Microscopic: units that can be resolved by an optical microscope (includes bacteria). (5) Macroscopic: all particles that can be resolved by the naked eye.
See fundamental particle; particle size.

particle accelerator. A device in which the speed of charged subatomic particles (protons, electrons) and heavier particles (deuterons, alpha particles) can be greatly increased by application of electric fields of varying intensity, often in conjunction with magnetic fields. It is possible to accelerate electrons and protons to speeds approaching the speed of light if sufficiently high voltage is used. Straight-line (linear) accelerators are used for protons, and doughnut-shaped betatrons for electrons; other types are the Van de Graaf electrostatic generator, the synchrotron, and the cyclotron. Before the development of nuclear reactors, the cyclotron was used to accelerate deuterons for use in bombarding stable nuclei to produce neutrons for inducing artificial radioactivity, fission, and formation of synthetic (transuranic) elements.
See betatron; cyclotron.

particle size. This term refers chiefly to the solid particles of which industrial materials are composed (carbon black, zinc oxide, clays, pigments, and the like). The smaller the particle, the greater will be the total exposed surface area of a given mass. Activity is a direct function of surface area; i.e., the finer a substance is, the more efficiently it will react, both chemically and physically. A colloidal pigment is a more effective colorant than a coarse one because of the greater surface area of its particles. A pound of channel carbon black has a surface area of 18 acres, which largely accounts for its powerful reinforcing effect in rubber. Thus, ultrafine grinding of powders is of utmost importance in such products as paints, cement, plastics, rubber, dyes, pharmaceuticals, printing inks, and numerous others.
See particle; surface chemistry; colloid chemistry; sedimentation.

particulate matter. Solid or liquid matter that is dispersed in a gas, or insoluble solid matter dispersed in a liquid, that gives a heterogeneous mixture.

parting agent. See abherent.

partition chromatography. The method of chromatography in which equilibrium is established between two liquid phases, one of which is held in the form of a gel.
See liquid chromatography.

partition function. An equation giving the distribution of molecules in different energy states in a system.

parylene. Generic name for thermoplastic film polymers based on *p*-xylylene and made by vapor-phase polymerization.
Derivation: *p*-xylene, $CH_3C_6H_4CH_3$, is heated with steam at 950C to produce the cyclic dimer di-*p*-xylylene, a solid that can be separated in pure form. The dimer is then pyrolyzed at 550C to produce monomer vapor of *p*-xylylene, $CH_2{:}C_6H_4{:}CH_2$, which is then cooled below 50C and condenses on the desired object as a polymer having the repeating structure $-(CH_2C_6H_4CH_2-)_n$, with n about 5000 and molecular weights of about 500,000. The polymer is used as a protective coating. Films as thin as 500 Å to 5 mils are obtained.
Use: Thin coatings of high purity and uniformity on almost any substrate that will resist a high vacuum, as paper, fabric, polyethylene and polystyrene film, ceramics, metals, many solid chemicals; electronic miniaturization systems; capacitors; thin film circuits.